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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,111	09/16/2003	Dolores Schendel	559412000200	6128

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MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/27/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/665,111	SCHENDEL ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *23-30 and 32-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *23-25,27-30,32-34 and 36-46* is/are rejected.

7)☐ Claim(s) *26 and 35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 9/29/06 ~~5/29/04~~. 4/29/04 KAC
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim 31 has been canceled. Claims 23, 27, 28, 29, 30, 32, 33, 34, 39 and 41 have been amended. Claims 43-46 have been added. Claims 23-30 and 32-46 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 41 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 24. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear how the active method step of claim 37 requiring that the HLA-haploidentical APC be "applied" fulfills the method objective of claim 23 requiring the generation of HLA-haploidentical APC. Claim 23 is simple drawn to the generation of the APC, not the application of the APC in a therapeutic treatment.

The rejection of claim 32 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in light of applicants arguments regarding the teachings of the specification on the usage of the composition as a treatment modality and the lack of contemplation of using said "vaccine" as a prophylactic vaccine.

The rejection of claims 27-30 under 35 U.S.C. 102(b) as being anticipated by Kugler et al (Nature Medicine, 2000, Vol. 6, pp. 332-336, reference of the IDS submitted April 29, 2004 is maintained. Claim 43 is also rejected for the same reasons of record

Kugler et al disclose a cell hybrid comprising a renal cell tumor and a dendritic cell from an allogeneic donor. The fused cell fulfills the specific embodiments of an antigen-presenting cell containing peptides from the renal cell carcinoma partner. Because the donor dendritic cells were fused with autologous tumor cells, it is reasonable to conclude that said cells would contain peptides present in at least two different tumor cell lines. When given the broadest reasonable interpretation, the cells of claims 27-31 carry no restrictions as to the identity of the recipient patient. The allogeneic dendritic cells disclosed by Kugler et al thus fulfill the embodiments of claim 27 because said cells would inherently have the property of being haploidentical with an unspecified patient.

Applicant argues that Kugler et al does not disclose the use of cells which are haploidentical to the patient to be treated. this has been considered but not found persuasive. Claims 27-31 are product claims and as such the intended use does not influence the prior art disclosure of Kugler et al. It is noted that the amendment to claim 27 encompasses APC into which proteins, peptides, RNA, DNA or cDNA encoding proteins or peptide which are over expressed in tumor cells has been introduced as an alternate embodiment to APC into which proteins, peptides, RNA, DNA or cDNA encoding proteins or peptide which are derived from autologous tumor cells. thus, the proteins and peptides which are introduced need not be autologous to that of the patient. The hybrid cell of Kugler et al thus remains inherently HLA-haploidentical to a individual which is HLA haploidentical to the donor of the dendritic cells used by Kugler et al. Applicant further argues that the Kugler reference was retracted and therefore it would not be available as a prior art reference due to lack of enablement. this has been considered but not found persuasive. The reference was retracted in September of 2003; however, the instant specification has an effective priority date of March 16, 2001, therefore as of the filing date the Kugler reference would be valid and relied upon of one of skill in the art.

Claims 23, 27, 28, 30, 31, 32, 40 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenman et al (WO 99/03976).

Claim 23 is drawn in part to a method for the generation of HLA-haploidentical a\APC for the treatment of tumor diseases in a patient comprising providing antigen-presenting cells

from a donor which are HLA-haploidentical with respect to that of the patient; introducing peptides which are over expressed in tumor cells or derived from autologous tumor cells into said HLA- haploidentical antigen-presenting cells. Claim 40 embodies the method of claim 23 wherein said antigen presenting cells are dendritic cells or macrophages
Claim 27 is drawn to the antigen-presenting cells obtained by a method according to claim 23. Claim 28 embodies the antigen presenting cells of claim 27 selected from carcinomas and hematopoietic cell tumors. Claim 30 embodies the cells of claim27 which are dendritic cells or macrophages. Claim 31 is drawn to a pharmaceutical composition containing HLA-haploidentical antigen-presenting cells. of claim 27.

Greenman et al teach a method of treating a population of isolated leukocytes from a donor so as to render a portion of the population non-proliferating to the extent that the population causes minimal GVHD while still retaining sufficient immune function effective to promote destruction of a diseased cell or pathogen (abstract). Greenman et al teach that antigen-presenting cells, which include dendritic cells (page 15, line 10), from donors can be pulsed with antigen characteristic of a diseased cell, or can be co-cultured with diseased cells(e.g., inactivated tumor cells); and these APCs can then be exposed to donor leukocytes prior to infusion of the donor leukocytes into a recipient (page 48, lines 1-4), which fulfills the requirement of introducing proteins or peptide which are over expressed in tumor cells into the donor antigen presenting cells . Greenman et al teach that the invention is useful for the treatment of chronic myelogenous, acute myelogenous, acute lympholytic, multiple myeloma and other forms of leukemia and myeloma, and the treatment of certain solid tumors, including breast lung, ovarian and testicular, prostate, colon, melanoma, renal carcinoma, neuroblastoma and head and neck tumors (page 19, lines 17-26), thus fulfilling the specific embodiments of claim 28. Greenman et al teach that a donor is identical genotypically in 3 or more of the 6 HLA loci of HLA-A, B, and DR. Greenman et al teach that the Graft-vs-Tumor or Graft versus Leukemia effect is separable from the pathogenic GVHD and that there are reported cases of cancer remission without onset of GVHD (page 3, lines 28 and lines 32-33). Greenman et al teach that in patients who are HLA "matched" with their donors (rather than HLA-identical) (page 16, lines 22-24).

It would have been prima facie obvious to provide HLA identical antigen-presenting cells from a donor which is HLA haploidentical to those of the patient. One of skill in the art would have been motivated to do so by the teachings of Greenman et al suggesting that the onset of GVHD is not required for the GVT or GVL therapeutic effect, and the recognition by Greenman et al of the use of HLA-identical donors. Further, Greenman et al do not teach against the instant invention as the requirement for a match in 3 or more of the 6 HLA loci of HLA-A, B, and DR does not exclude a match at all of HLA-A, B, C, DR, DQ, and DP.

Applicant argues that Greenman et al do not contemplate using a HLA-identical match. this has been considered but not found persuasive. Greenman et al do not teach against a complete match, but provides preferred embodiments for less than a complete match in cases where the patient lacks a HLA-identical donor (page 27, lines 3-6).

Claims 23, 25, 27, 28, 30, 31, 32, 33, 34, 38, 39, 40, 43, 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenman et al (WO 99/03976) in view of Nair et al (WO 97/41210).

Greenman et al render obvious the generation of T cells ex vivo for administration to a patient with a tumor comprising contacting the T cells of the individual with a dendritic cell pulsed with tumor peptides, wherein said dendritic cell is HLA-haploidentical to the patient, and the administration of the activated T cells to the patient. Greenman et al do not teach the administration of the dendritic cells pulsed with the tumor peptides or the introduction of RNA or cDNA encoding tumor peptides into the dendritic cell.

Nair et al teach method for the loading of dendritic cells by introduction of a tumor associated RNA which is unfractionated or cDNA made by PCR (page 3, lines 13-19). Nair et al disclose that the method offers advantages in that there is no need to identify specific tumor rejection antigens and an immune response to unfractionated RNA or cDNA made therefrom elicits immune responses to several tumor antigens reducing the likelihood of escape mutants and extends the use of active immunotherapy to the treatment of cancers for which specific tumor antigens have not yet been identified which is the vast majority of cancers (page 9, lines 21-35). Nair et al teach a method for treating cancer comprising directly administering the loaded dendritic cells to a patient suffering from cancer (claims 51-53).

It would have been prima facie obvious at the time the claimed invention was made to administer the RNA or cDNA loaded dendritic cells in addition to the T cell activated ex vivo to a patient having cancer. One of skill in the art would have been motivated to do so by the teachings of Nair et l regarding the improvements associated with using unfractionated RNA for the loading of dendritic cells, and the administration the loaded dendritic cells as part of the immunotherapy as taught by Nair et al. It is noted that the unfractionated RNA and cDNA made therefrom of Nair et al would inherently comprise the tumor defined antigens of claim 45.

Claims 23-25, 27-30, 32-34, 37-46 rejected under 35 U.S.C. 103(a) as being unpatentable over Greenman et al and Nair et al as applied to claims 23, 25, 27, 28, 30, 31, 32, 33, 34, 38, 39, 40, 43, 44 and 45 above, and further in view of Storkus et al (U.S. 6,077,519).

Claims 24 and 41 embody the method of claim 23 wherein proteins, peptide, RNA, DNA or cDNA from several different tumor cell lines are introduced into the HLA-haploidentical APC. Claim 42 embodies the method of claim 41 wherein pooled cDNA from two or three different tumor cell lines is introduced.

Claim 29 embodies the pharmaceutical composition of claim 27 wherein the HLA-APC comprises proteins, peptides, RNA, DNA or cDNA from several different tumor cell lines.

Claim 37 embodies the method of claim 23 in that the HLA-APC are applied by intravenous, Sub-Q or I.M. routes.

Claim 46 embodies the method of claim 45 wherein the tumor antigens are Her2/neu, PSMA, WT-1, MUC-1 or telomerase.(prostate cells).

The combination of Greenman et al and Nair et al render obvious the instant invention regarding the loading of haploidentical APC with unfractionated RNA or cDNA made therefrom from tumor tissue from the patient (Nair et al, page 3, lines 29-30). The combination does not teach or suggest the use of multiple tumor cell lines as a source of peptides, RNA or cDNA for loading or pulsing dendritic cells.

Storkus et al teach that dendritic cells can be pulsed with HLA-attached allogeneic tumor cell lines as an alternative to acid eluted peptides from the patients tumor cells (column 12, lines 21-32). Storkus et al teach the administration of pulsed dendritic cells by intravenous routes (column 35, lines 53-60). Storkus et al teach that the invention be applied to treat colon,

squamous, gastric, breast, prostate, lung, cervical and ovarian carcinomas. It is noted that prostate carcinomas would inherently express prostate specific membrane antigen.

It would have been prima facie obvious at the time the claimed invention was made to use pooled tumor cell acid eluted peptides or RNA or cDNA for pulsing or loading the dendritic cells used in the methods rendered obvious by the combination of Greenman et al and Nair et al. One of skill in the art would have been motivated to do so by the suggestion of Storkus et al that cell lines can be used as a source of tumor specific antigen peptides. One of skill in the art would have been motivated to look to this source in the event that no tumor material from the patient was available or insufficient. One of skill in the art would have been motivated to used pooled acid eluted peptides or unfractionated RNA or unfractionated cDNA from several different tumor cell lines because of the teachings of Nair et al regard tumor escape mechanisms. One of skill in the art would understand that providing a multitude of antigens to the dendritic cell would compensate for the ability of a tumor to down regulate an antigen and escape immune surveillance. The more tumor specific antigens which can be expressed by the activated dendritic cells, the more populations of activated T cells will be available for recognition of tumor cells. Further, because the method is taught by Storkus et al to extend to the treatment of prostate cancer, the unfractionated RNA, cDNA made therefrom would inherently include prostate specific membrane antigen, PSMA, thus fulfilling the limitation of claim 46.

Claims 26 and 35 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 23-42 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-20 of copending Application No. 10/663,421 is withdrawn in light of abandonment of the application.

All other rejections and objections as set forth in the priorOffice action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A Canella, Ph.D.
11/10/2006